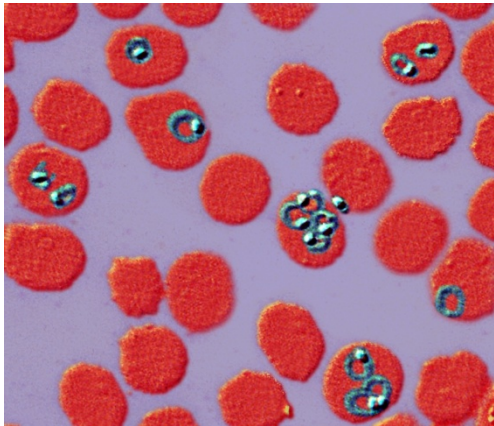


Why are malaria parasites so successful?

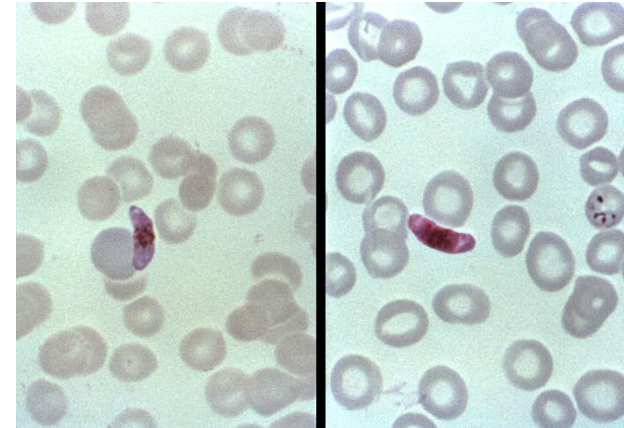
Julian Rayner
Sanger Institute Malaria Programme
julian.rayner@sanger.ac.uk



What causes malaria?

Parasite

- Single cell eukaryotic parasite of the *Plasmodium* genus
- Four species of malaria cause malaria in humans: *P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae*

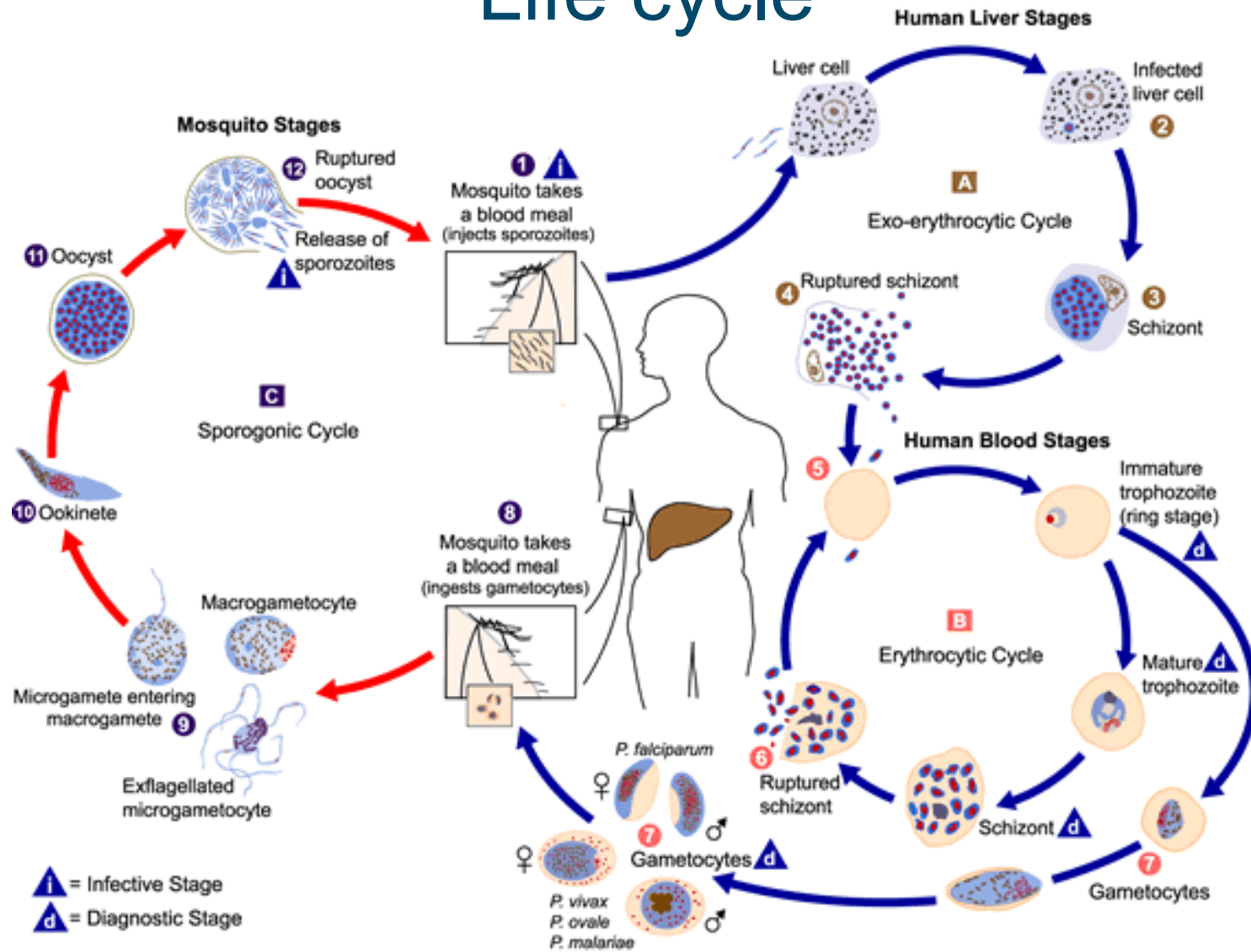


And vector

- Mosquitoes of the *Anopheles* genus, not any others
- Parasite must cycle through both to complete life cycle, so can be attacked at either stage



Life cycle



It's not just us that are affected by malaria

Image source: CDC DPDx

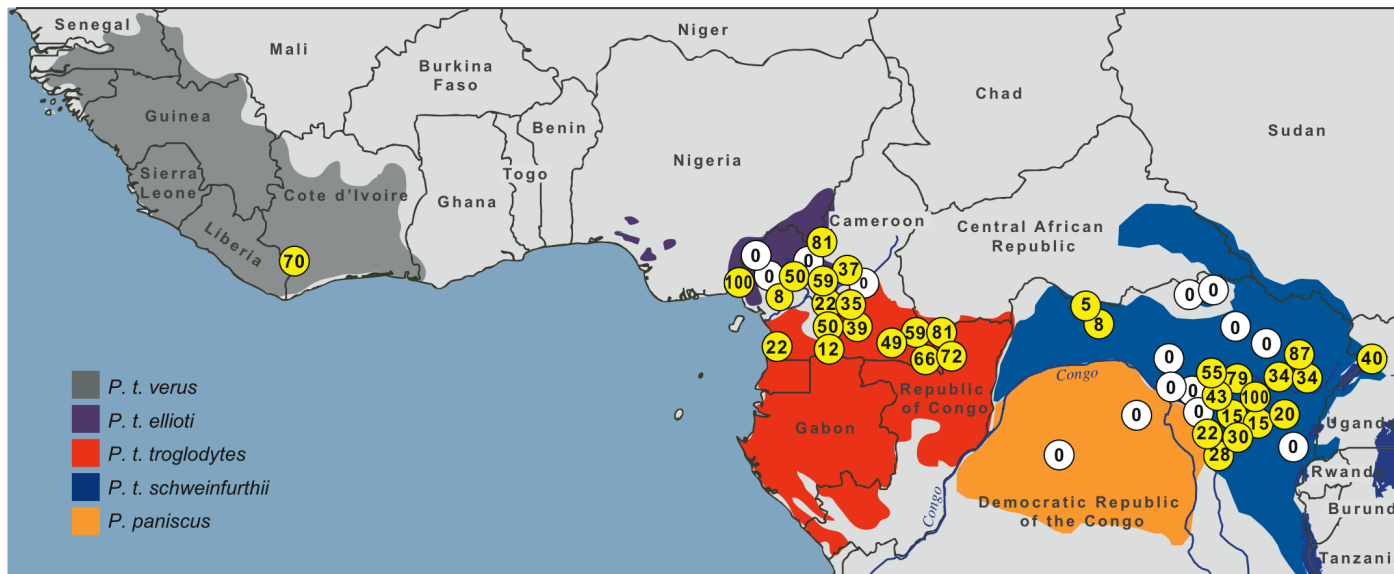
malaria programme



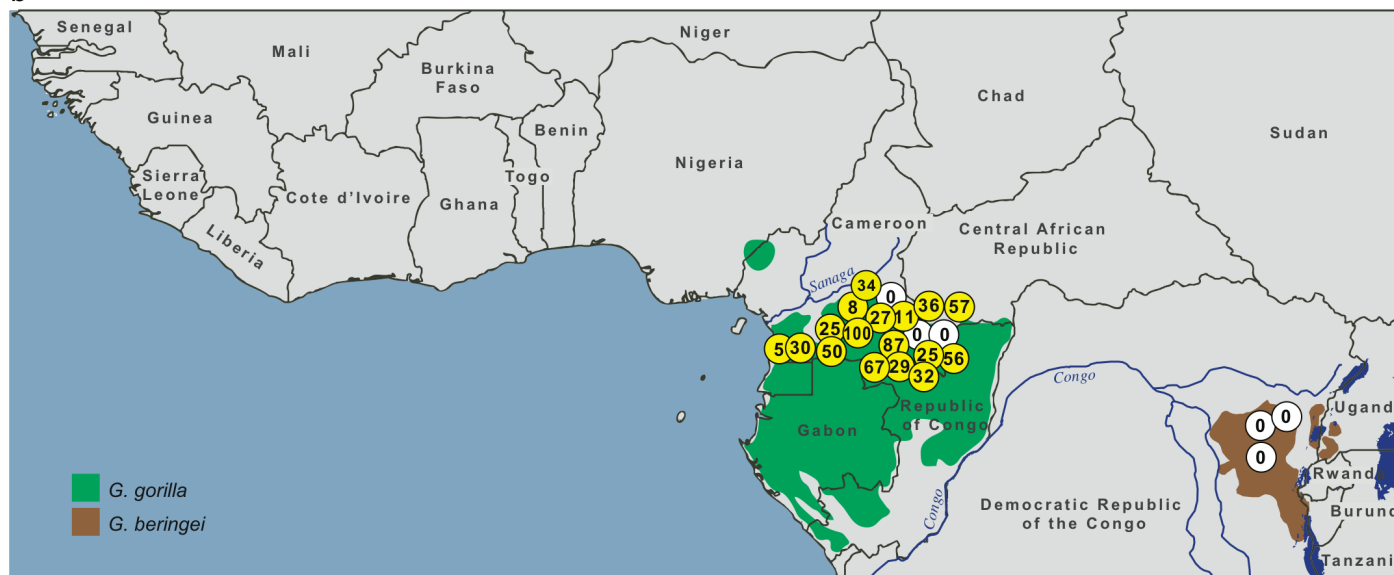
Western lowland gorillas (*Gorilla gorilla*) foraging in the Central African Republic.
(photo courtesy of Ian Nichols and the National Geographic Society)

malaria programme

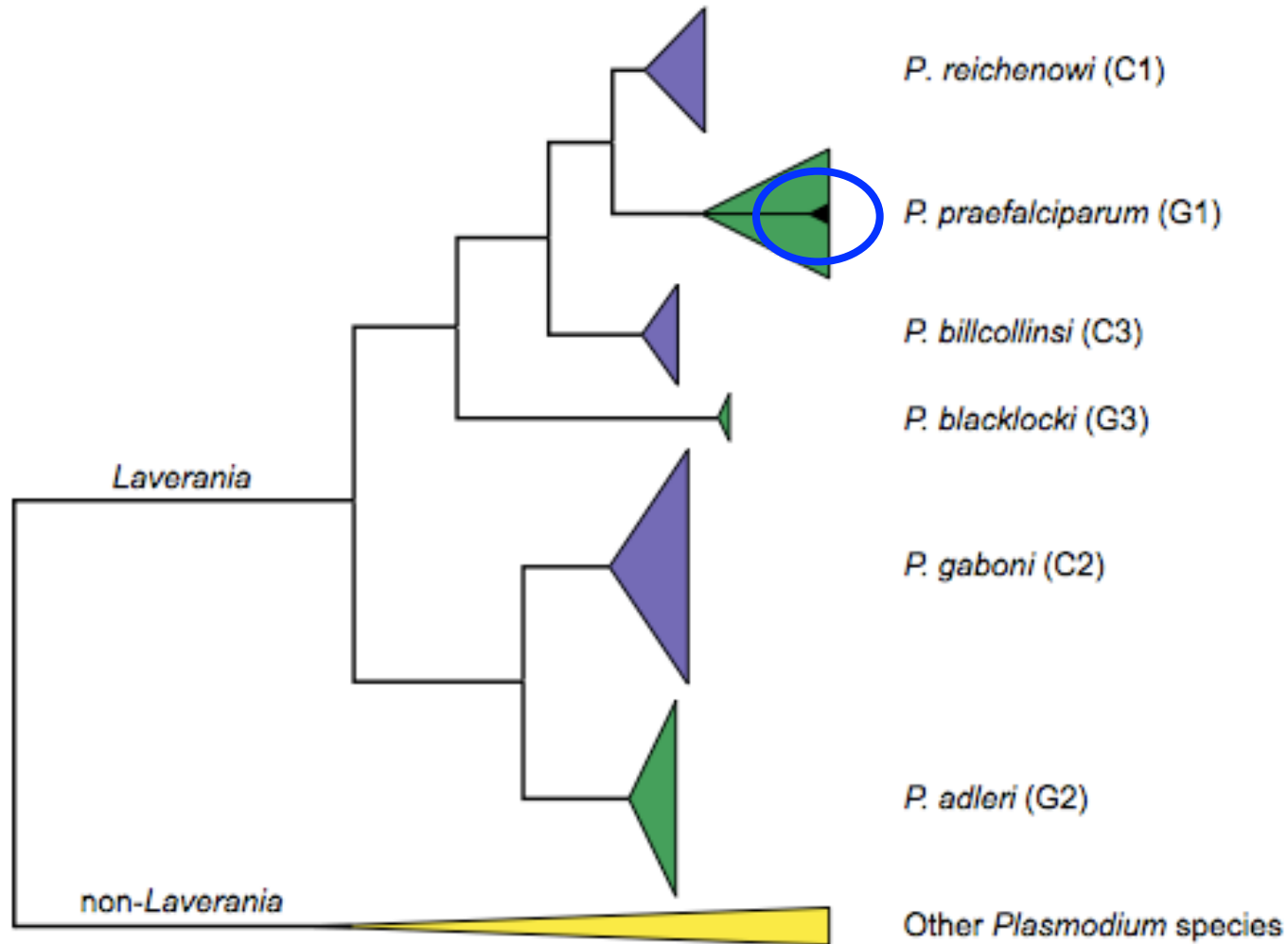
a



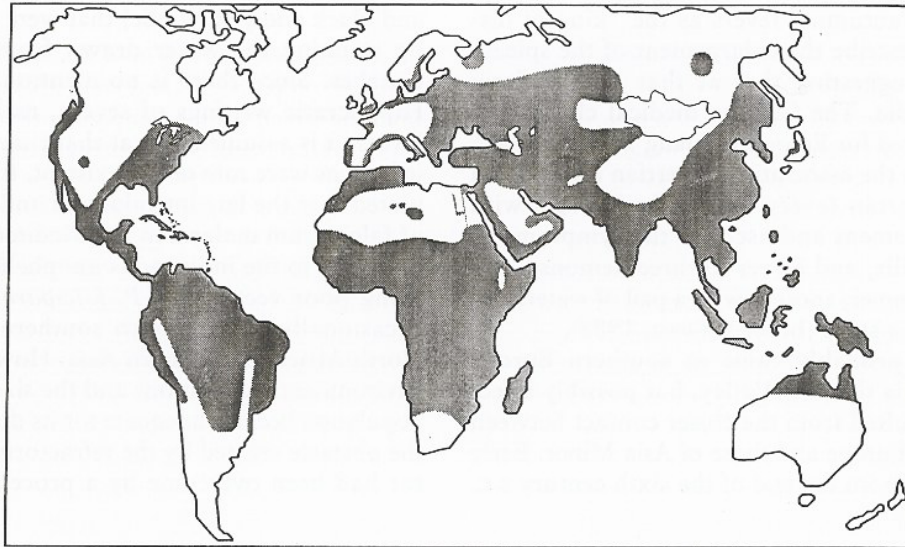
b



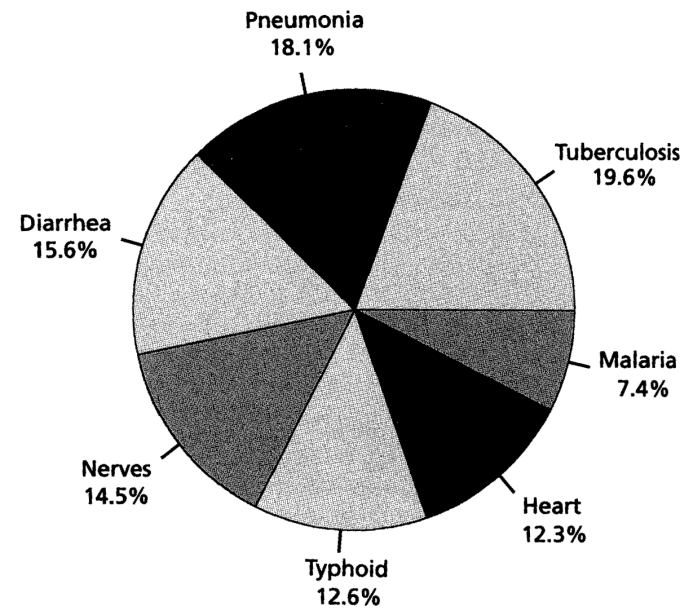
malaria programme



Malaria - start of last century



- Records of malaria-like illness in ancient Greece, Rome
- Global spread c. 1900 - note UK, Europe, southern US
- What is the picture like today?



- Mortality figures, Alabama c. 1900

malaria programme

Chelsea's Didier Drogba to face Fulham despite having malaria

- Striker may have had malaria since January
- Medication should beat illness in 48 hours

Dominic Fifield

guardian.co.uk, Tuesday 9 November 2010 22:29 GMT

[A larger](#) | [smaller](#)



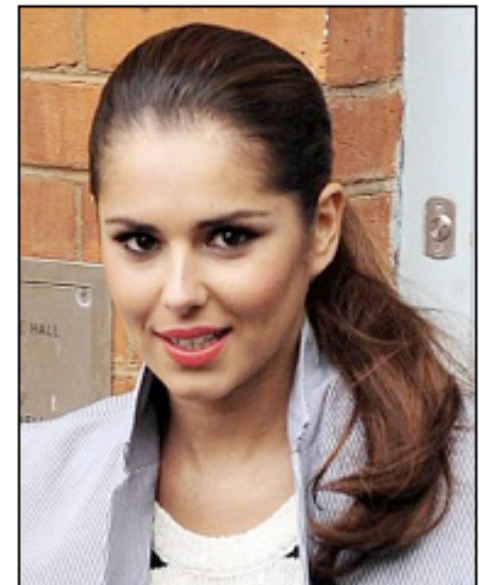
Didier Drogba is suffering from malaria. Photograph: Andrew Yates/AFP/Getty Images

Didier Drogba will start Chelsea's west London derby against Fulham tomorrow evening despite suffering from malaria. Blood tests on Monday evening revealed the Ivory Coast forward, who missed last month's games against Aston Villa and Spartak Moscow through illness and has not seemed fully fit since, had contracted the tropical disease.

Simon Cowell on Cheryl Cole's malaria battle: 'It was a nightmare'

By RACHEL QUIGLEY

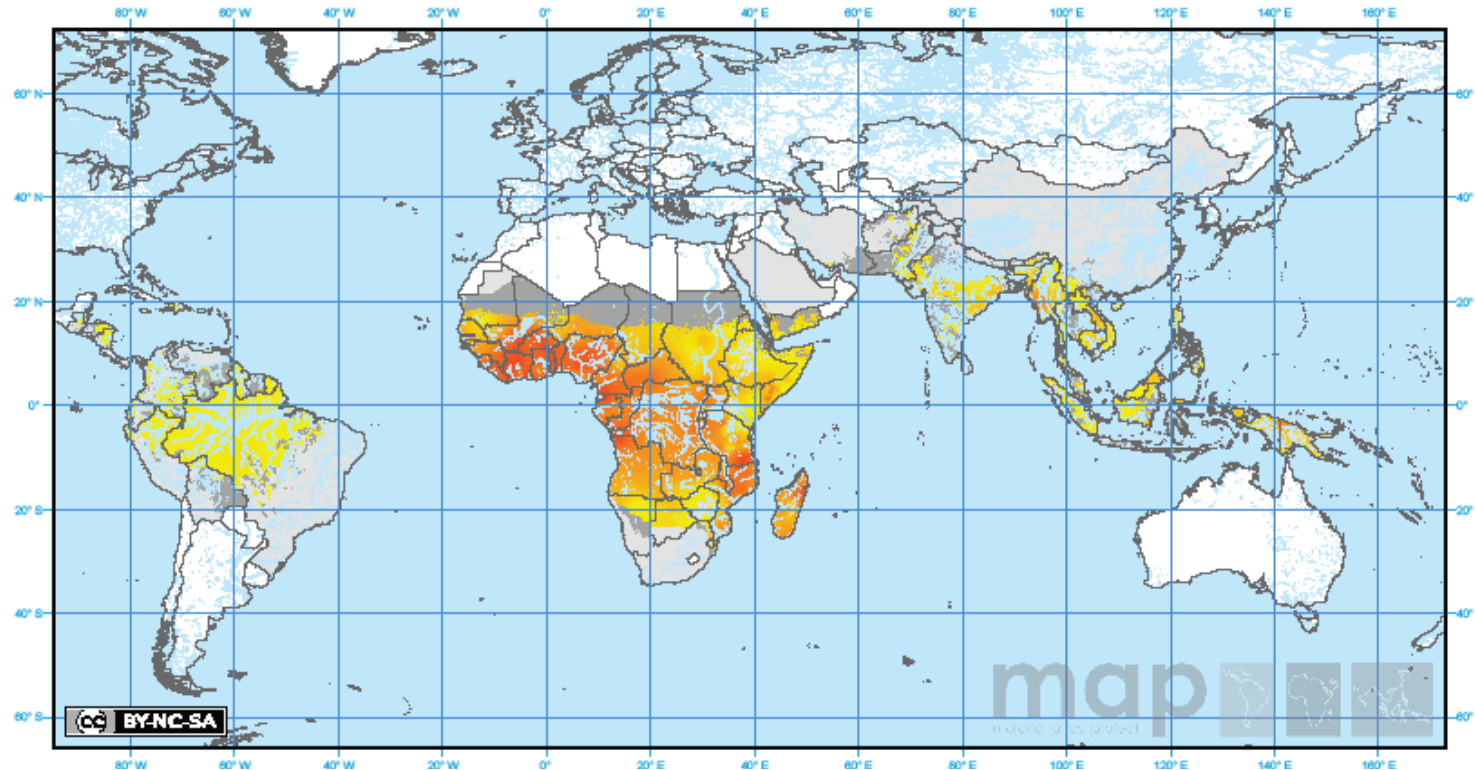
Last updated at 5:51 PM on 14th September 2010



Scare: Simon Cowell, pictured over the weekend, has spoken of his relief of Cheryl Cole's recovery from malaria

'I didn't know much about malaria but apparently it was the really serious strain of it. We were really worried. But look, this is real life. People get sick, but unfortunately she got very sick and you've got to deal with it. This is what making reality TV is all about.'

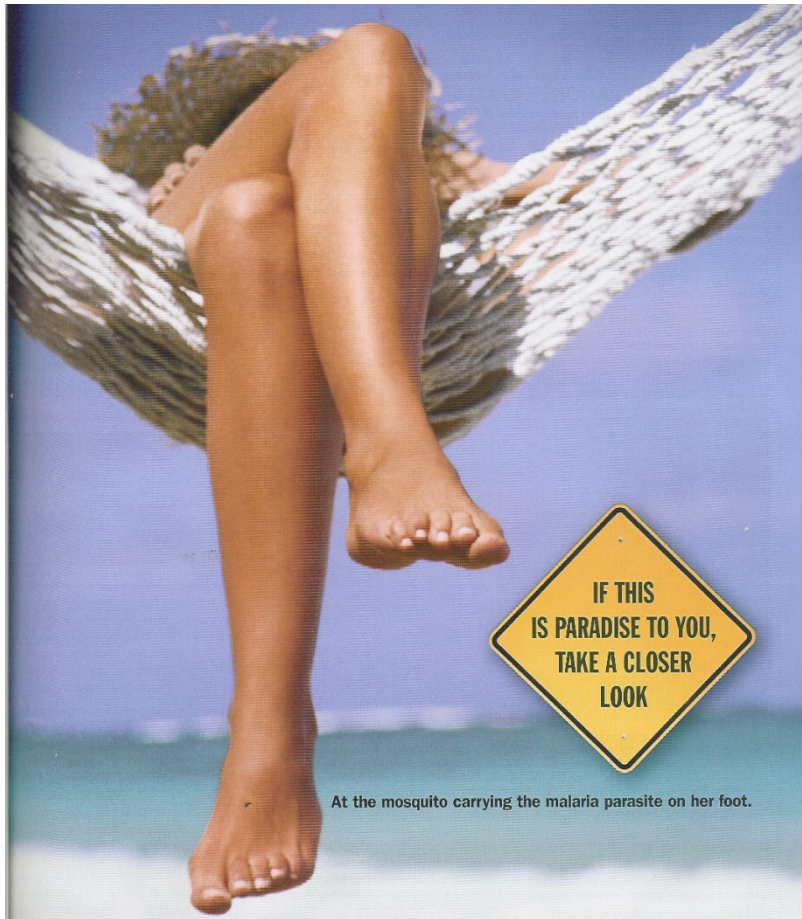
Malaria – Today



- 40%+ of the world's population at risk
- 300 - 500 million infected
- >1 million deaths, largely in children in Africa
- Widespread drug resistance, no vaccine

Image licensed to the Malaria Atlas Project (MAP; www.map.ox.ac.uk) by Hay, S.I. et al. (2009). A world malaria map: *Plasmodium falciparum* endemicity in 2007. *PLoS Medicine* 6(3): e1000048.

malaria programme



At the mosquito carrying the malaria parasite on her foot.

Each year, more than 125 million international travelers visit countries where malaria is present. Are you protected? Be smart, take MALARONE. MALARONE is 98% effective in the prevention of the most common and deadly form of malaria (*Plasmodium falciparum*) and generally well tolerated.* No wonder MALARONE is now the #1 prescribed antimalarial product in the U.S. Ask your doctor if MALARONE is right for you. For more information, and to download a \$20 rebate for MALARONE, visit Travelsafely.com.

Travel Smart
MALARONE tablets
atovaquone and proguanil HCl

For the prevention of malaria: *The most common side effects in adults included headache and abdominal pain, and additionally vomiting in children. You should not take MALARONE if you have severe kidney disease or are allergic to MALARONE or any of its components. Rare cases of anaphylaxis (a serious allergic reaction) in treatment with MALARONE have been reported. Please see important information on the following page.

How does the parasite make this work?

1. Evade the immune response
2. Adapt to different hosts



Evasion approach 1: Go intracellular



Movie credit: D. Berry, <http://www.wehi.edu.au/wehi-tv/>

malaria programme

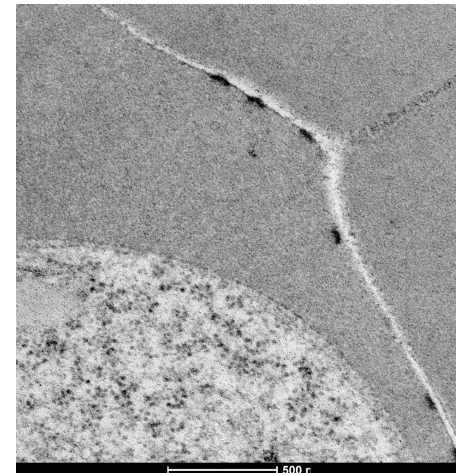
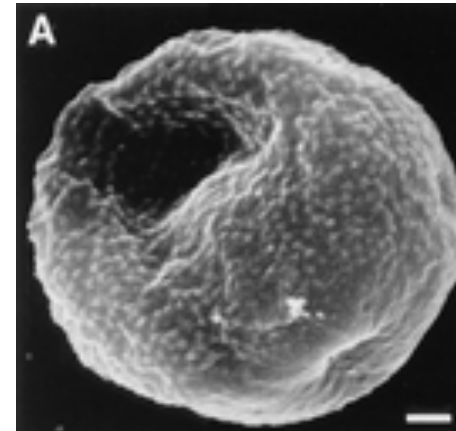
Evasion approach 2: Avoid the spleen



malaria programme

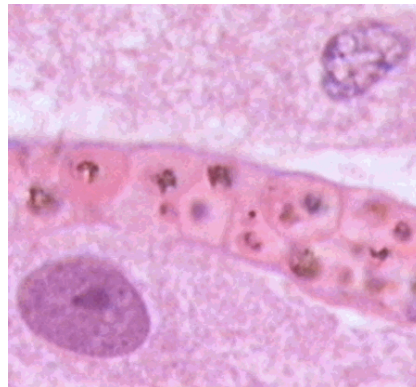
Cytoadherence depends on modifications of the infected erythrocyte

Monkeys	Parasitemia (%)	Drug treated
FCR-3 wild type, intact		
115 (M, II)	4.1	Yes
5335 (F, II)	6.5	Yes
5336 (F, III)	5.5	Yes
7921 (F, II)	0.8	Yes
8443 (M, II)	2.4	Yes
FCR-3 wild type, splenectomized		
217J (F, II)	4.4	Yes
Clone D3, intact		
6902 (M, II)	0	No
8490 (M, II)	0	No
WR 159 (M, II)	0	No
5342 (F, II)	0.02	No
114 (F, IV)	0	No
216J (F, III)	0.005	No
WR 157 (F, IV)	0	No
Clone D3, splenectomized		
209J (M, III)	7.6	Yes
WR 135 (M, IV)	2.9	No
5341 (F, III)	7.6	Yes

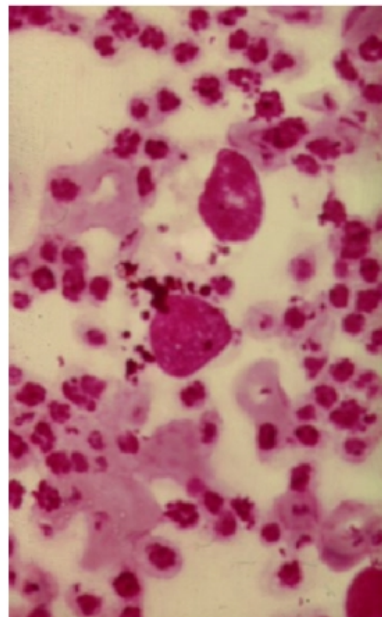


Good for the parasite, bad for us...

Cytoadherence is also linked to pathology

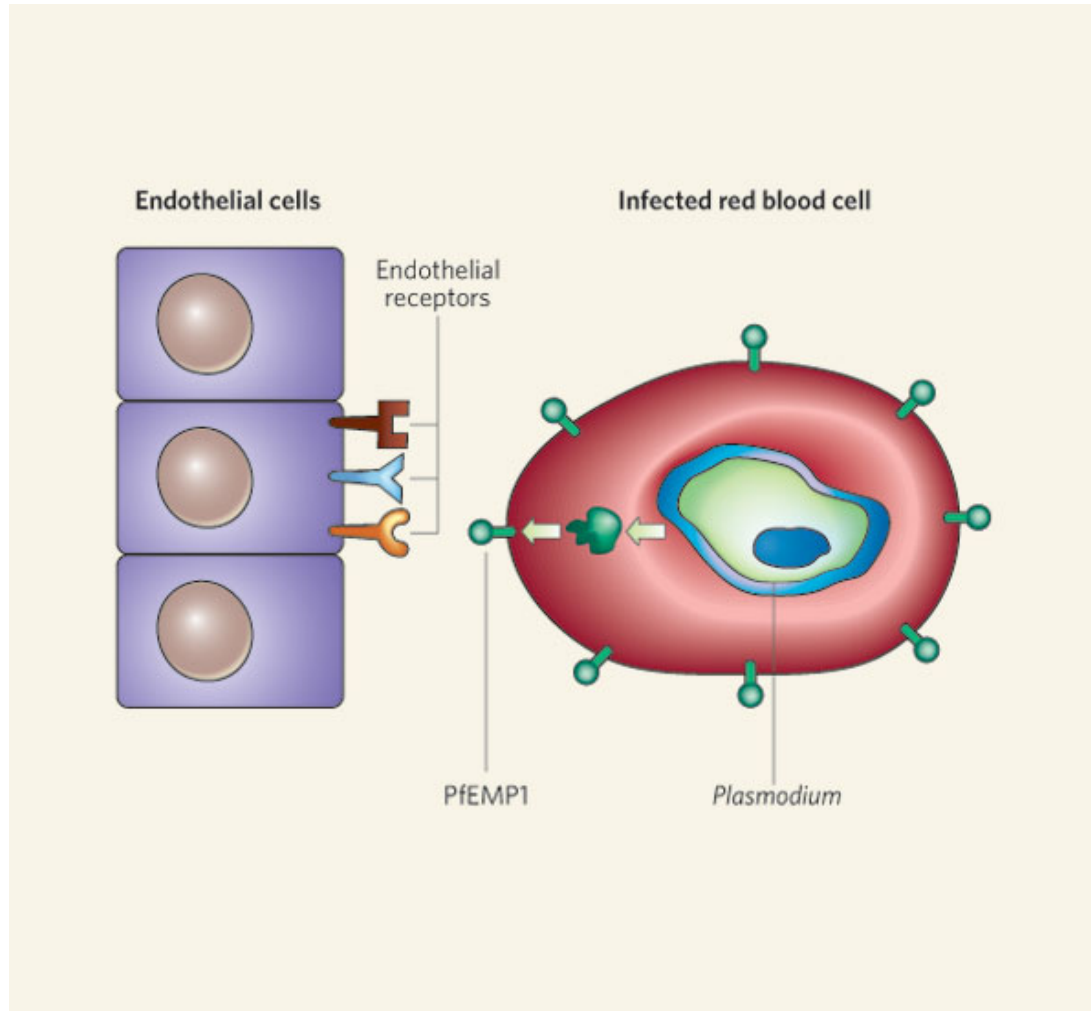


- Cerebral malaria – impaired consciousness/coma, major cause of malaria mortality
- Associated with adherence of infected erythrocytes in brain microvasculature



- Pregnancy associated malaria – reduced nutrient/oxygen uptake to fetus, cause of still birth and low birth weight babies
- Associated with adherence of infected erythrocytes in placenta, sometimes up to 90% of RBCs

How does cytoadherence work?

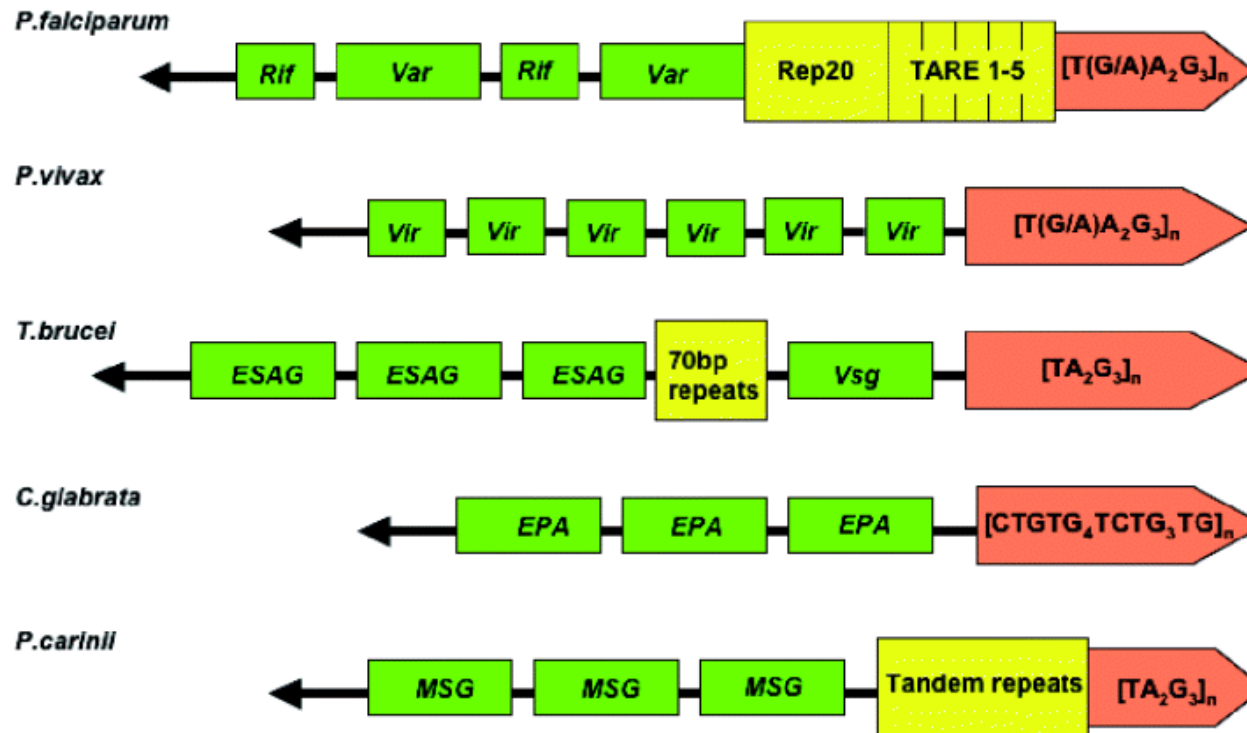


- Parasites express ligands on the surface of infected erythrocytes that bind to endothelial cells

- But doesn't that defeat the whole purpose of being intracellular?

malaria programme

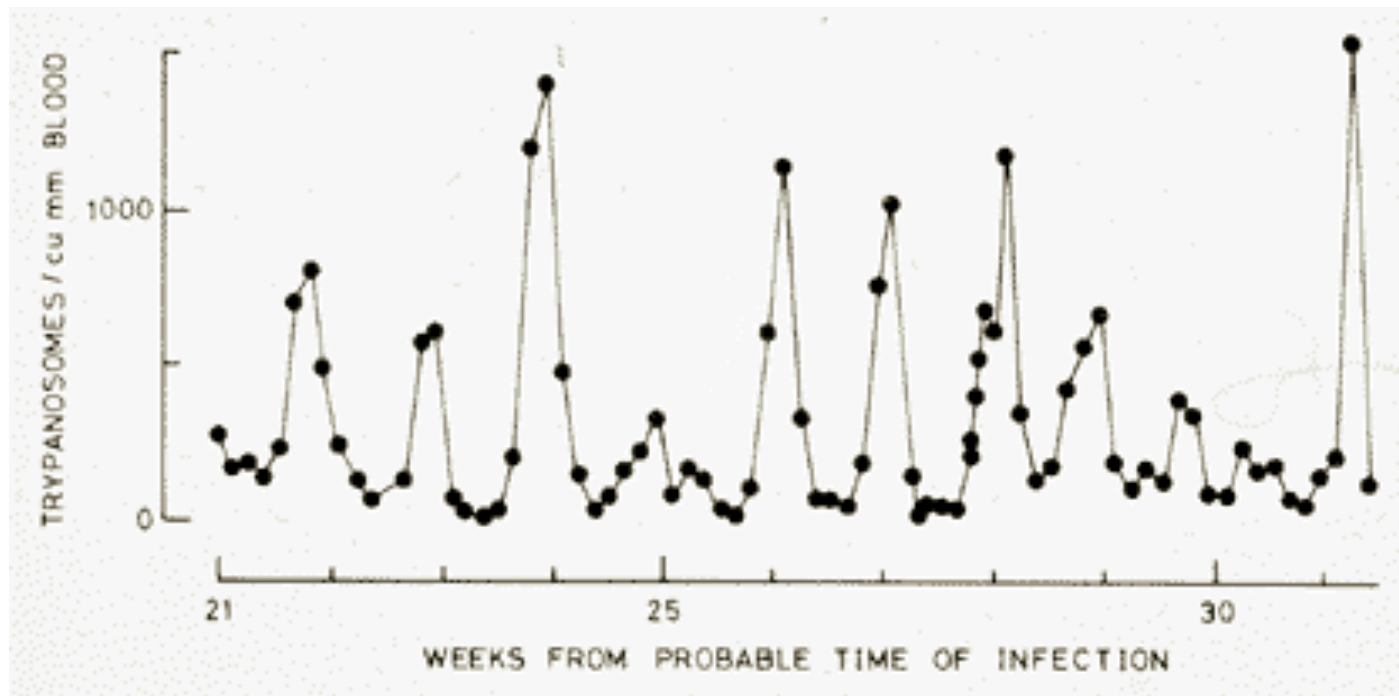
Need multiple variable adhesive proteins



- *P. falciparum* has multiple *var* genes (59)
- Near the ends of chromosomes, so frequent recombination
- Expresses only one at a time, and switches between them

malaria programme

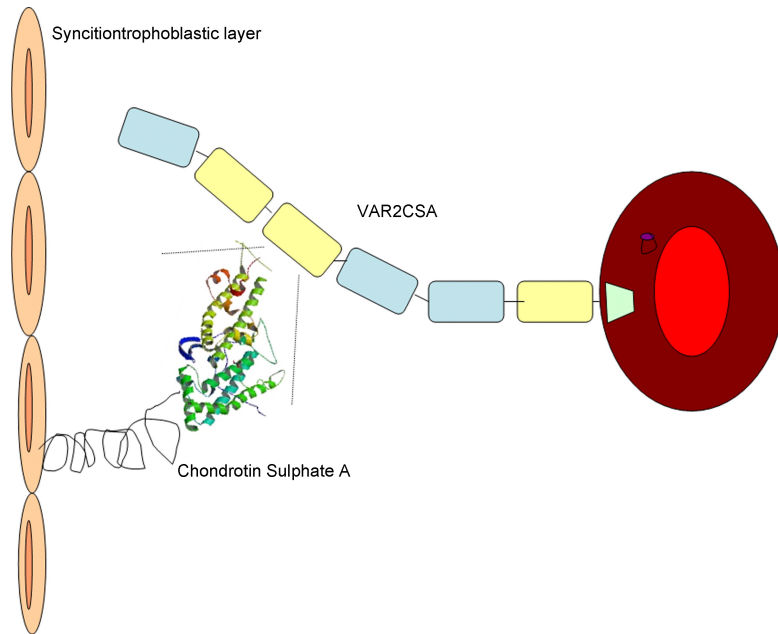
What do you get? Antigenic variation



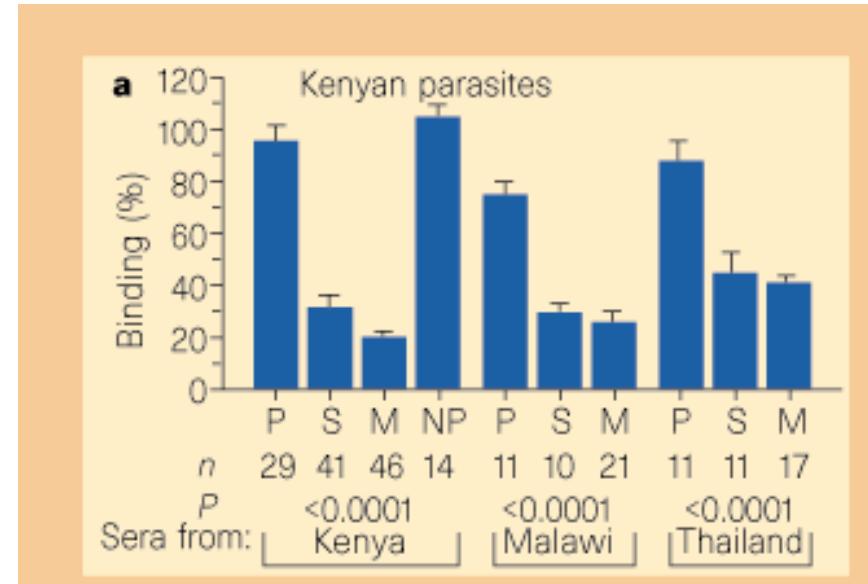
- Immune system adapts to one variant and clears it out
- Small number of parasites that have switched to a distinct variant escape, and start a new infection
- Result is chronic waves of infection, unless something kicks off severe complications

malaria programme

Expression of specific vars associated with pathology

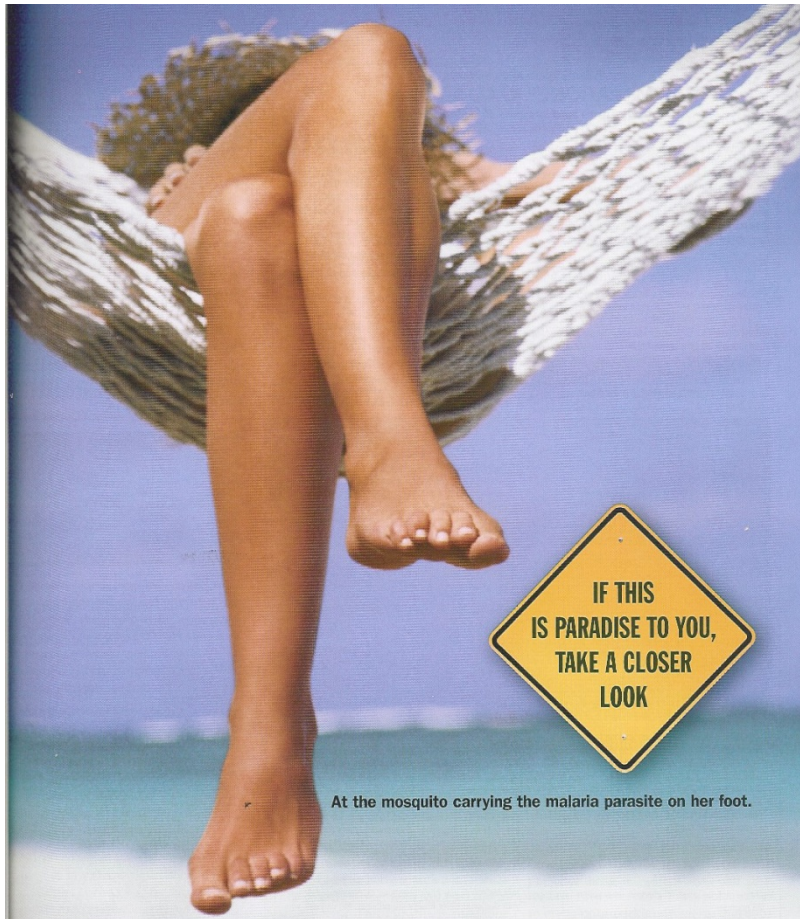


- Var2CSA expression associated with *P. falciparum* strains isolated from placenta
- Binds a modified version of CSA found primarily in the placenta



- Repeated exposure to var2CSA may explain declining rates of placental malaria in later pregnancies

malaria programme



At the mosquito carrying the malaria parasite on her foot.

Each year, more than 125 million international travelers visit countries where malaria is present. Are you protected? Be smart, take MALARONE. MALARONE is 98% effective in the prevention of the most common and deadly form of malaria (*Plasmodium falciparum*) and generally well tolerated.* No wonder MALARONE is now the #1 prescribed antimalarial product in the U.S. Ask your doctor if MALARONE is right for you. For more information, and to download a \$20 rebate for MALARONE, visit Travelsafely.com.

Travel Smart
MALARONE^{tablets}
atovaquone and proguanil HCl

For the prevention of malaria: *The most common side effects in adults included headache and abdominal pain, and additionally vomiting in children. You should not take MALARONE if you have severe kidney disease or are allergic to MALARONE or any of its components. Rare cases of anaphylaxis (a serious allergic reaction) in treatment with MALARONE have been reported. Please see important information on the following page.

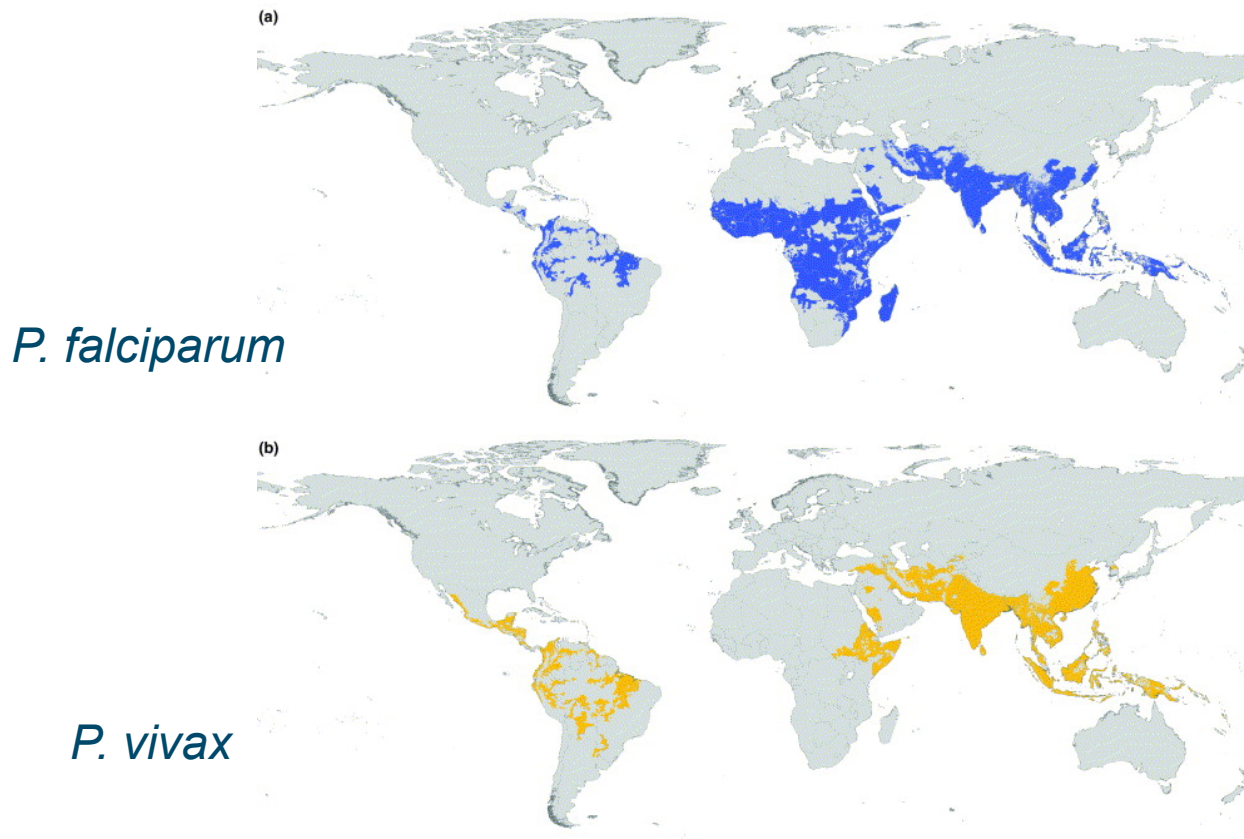
How does the parasite make this work?

1. Evade the immune response
2. Adapt to different hosts



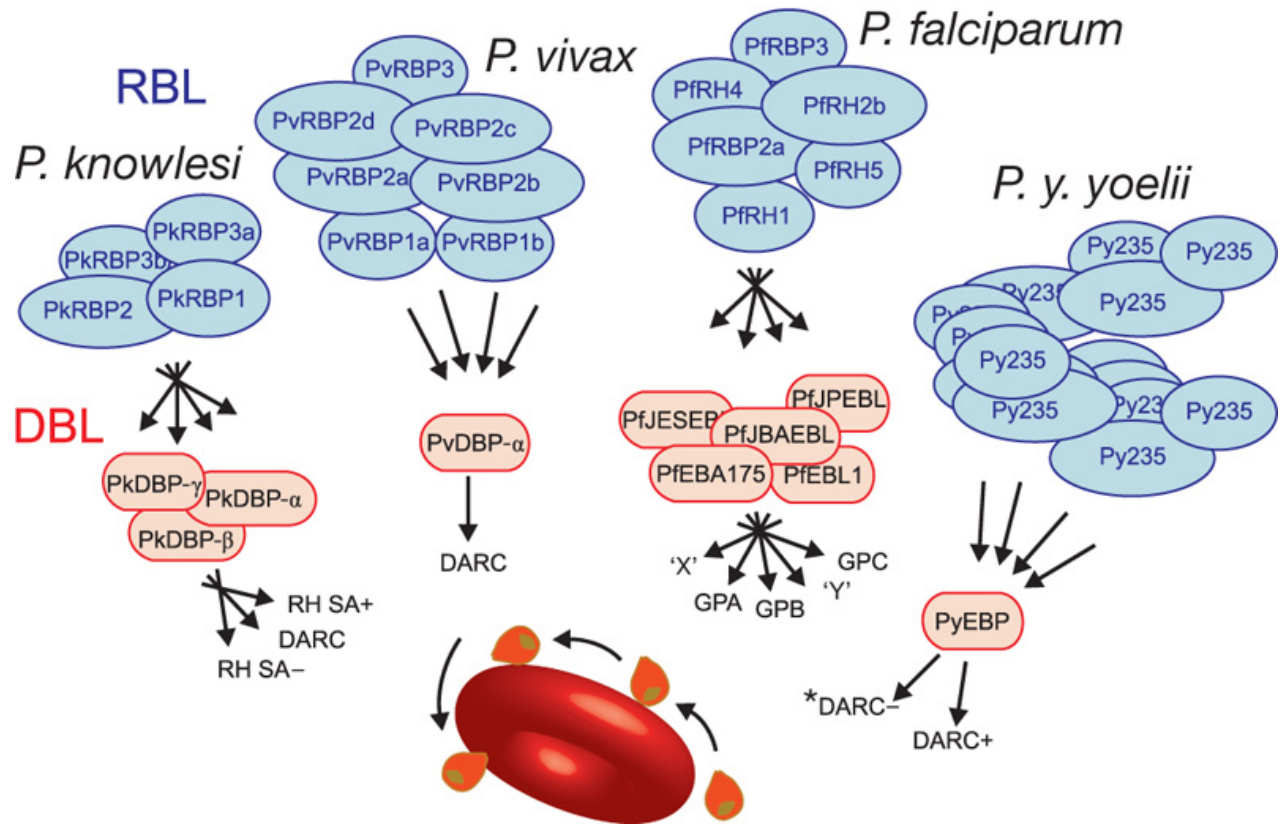
malaria programme

Some *Plasmodium* parasites are quite restricted



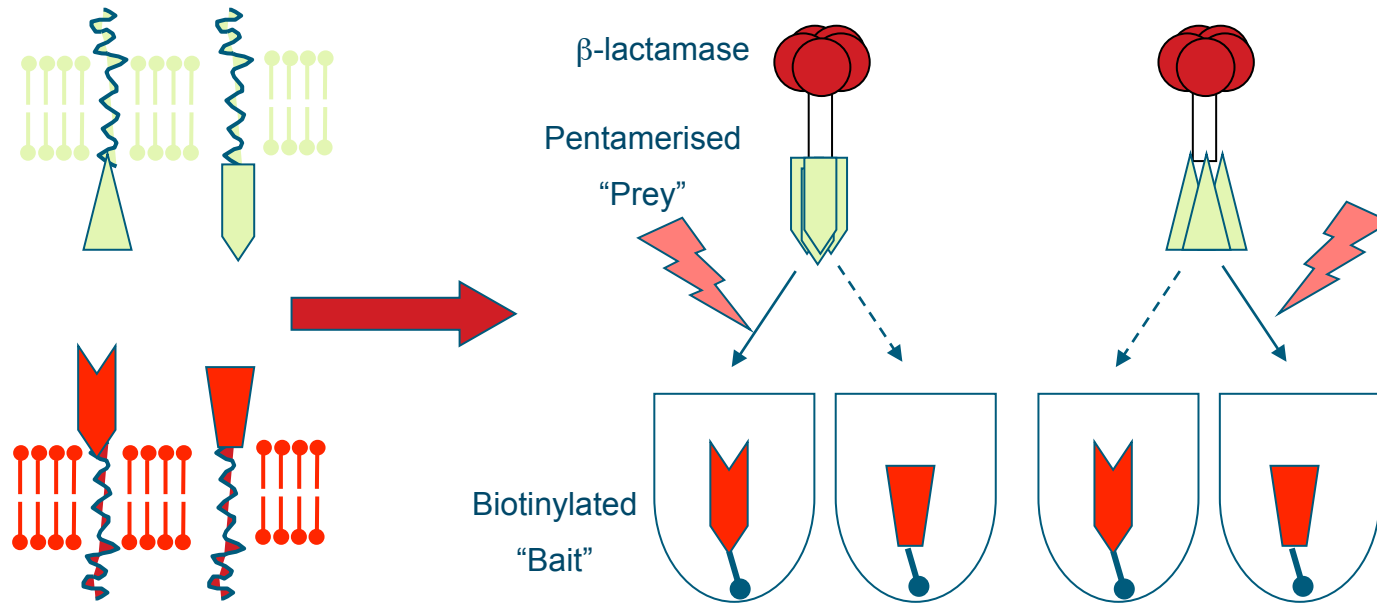
Absence of *P. vivax* in West Africa is due to human genetic variation - Duffy negativity prevents *P. vivax* erythrocyte invasion

malaria programme



- *P. falciparum* has multiple erythrocyte recognition molecules, more adaptable
- How do we know what binds to what, and therefore what would make a good target?

AVEXIS: A tool to detect extracellular interactions



- Cell-cell interactions have very low affinity, hard to detect.
- Sanger-developed technology (AVEXIS, Gavin Wright) gets around the problem.

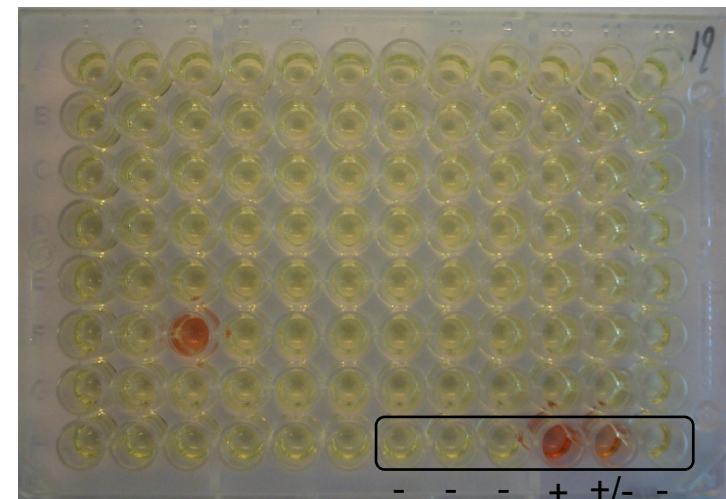
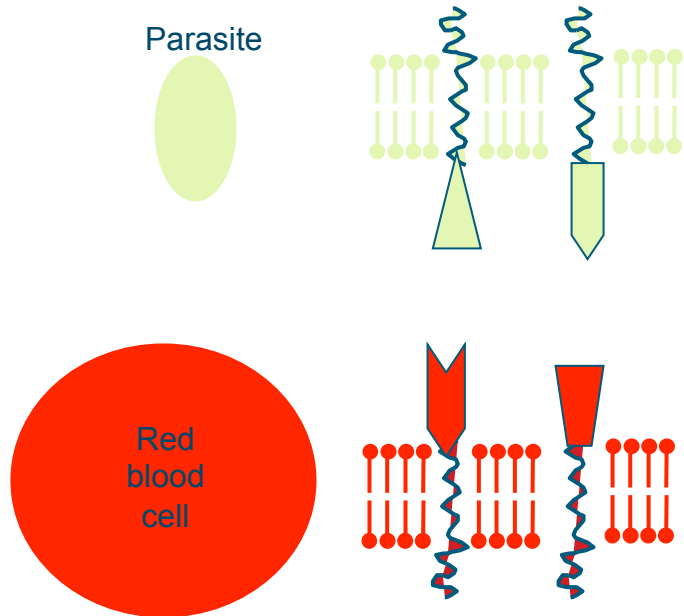


Image credits: G. Wright

controls: - - - + +/ -

malaria programme

Applying AVEKIS to *Plasmodium* invasion



- Approach: use genome lists and expression data to identify proteins expressed on *P. falciparum* surface and human RBC surface
- Express whole sets of proteins (50+)
- Test what binds to what in all vs. all assays

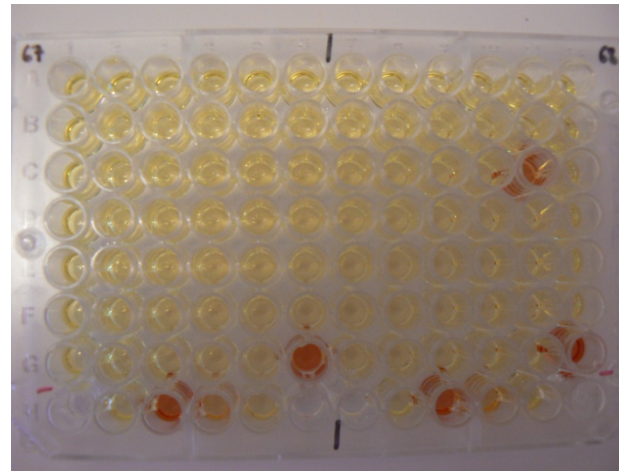
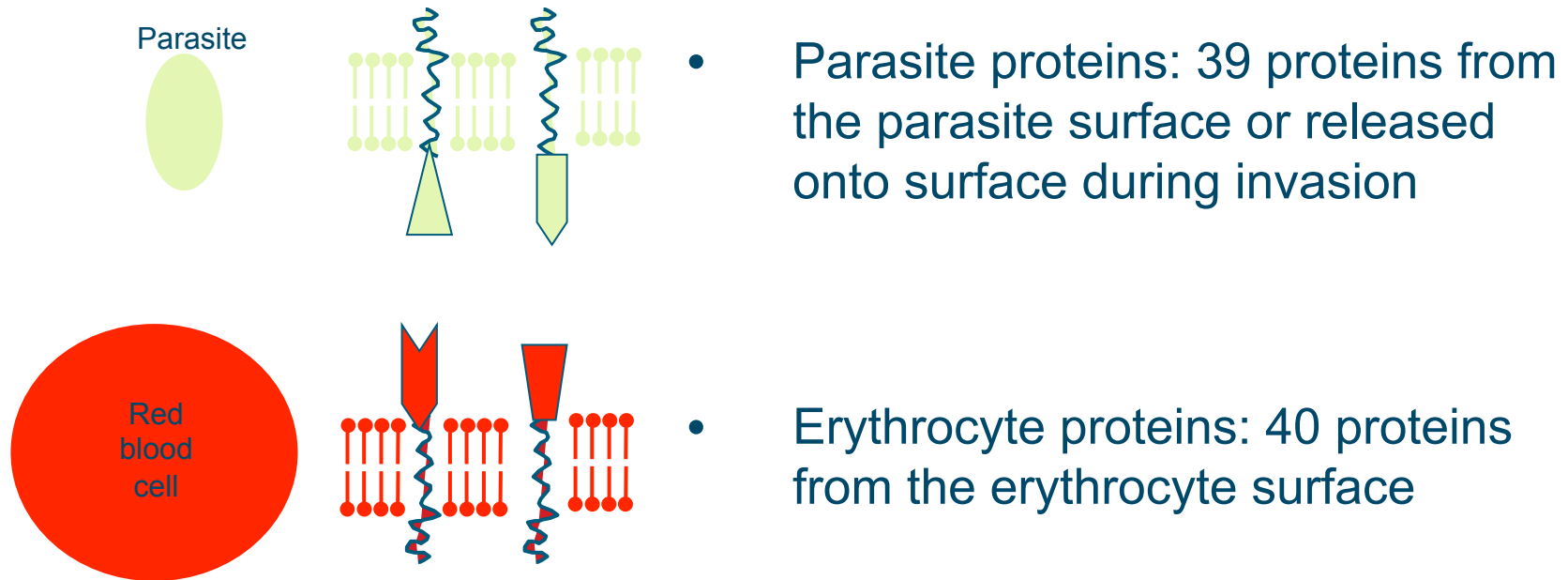


Image credits: G. Wright

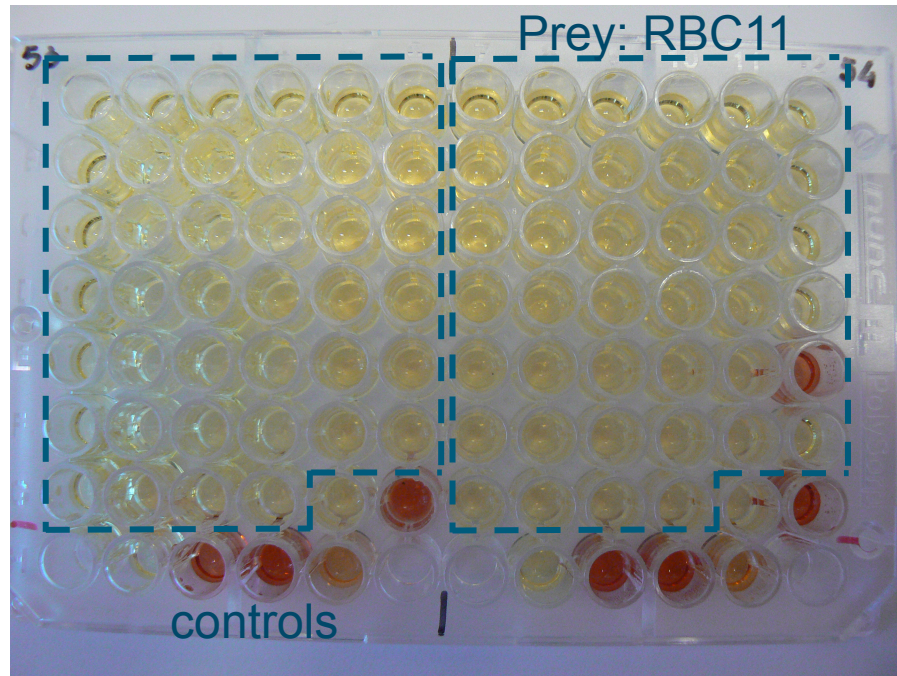
Applying AVEXIS to *Plasmodium* invasion



- Extracellular domains expressed as recombinant proteins
- Erythrocyte and parasite proteins expressed against each other in all vs. all manner using AVEXIS

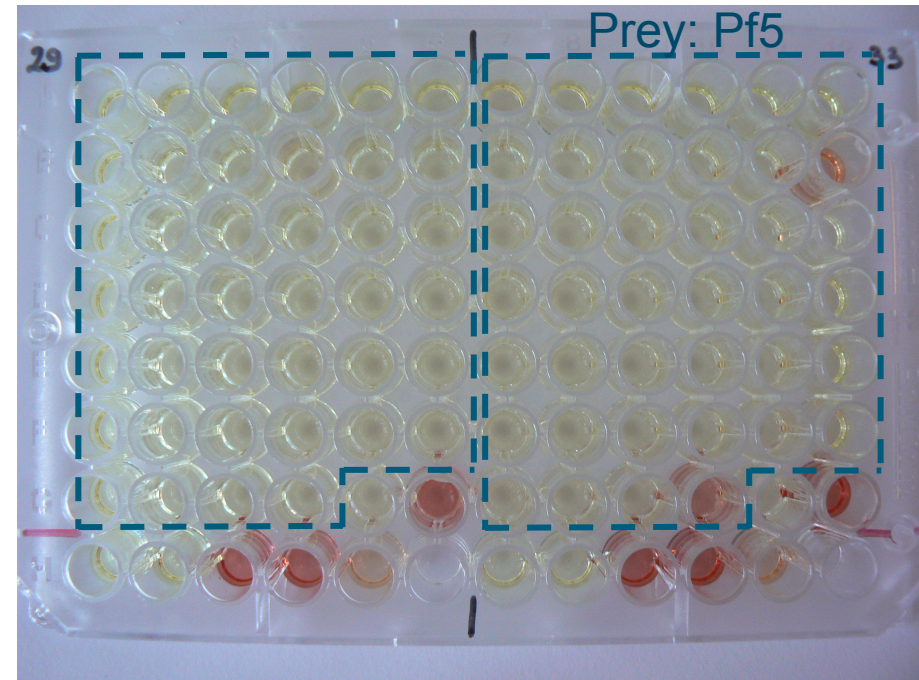
malaria programme

Erythrocyte preys screening
merozoite bait arrays



Bait: Pf5 – well E12

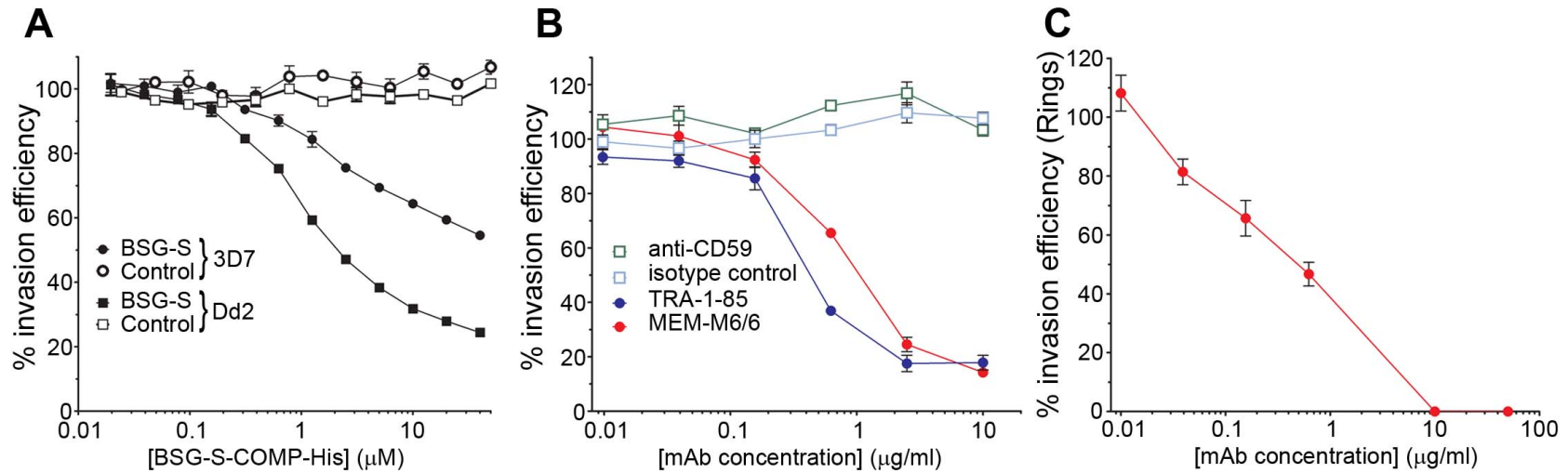
Merozoite preys screening
erythrocyte bait arrays



Baits: RBC11 – well B12
RBC11 – well G10

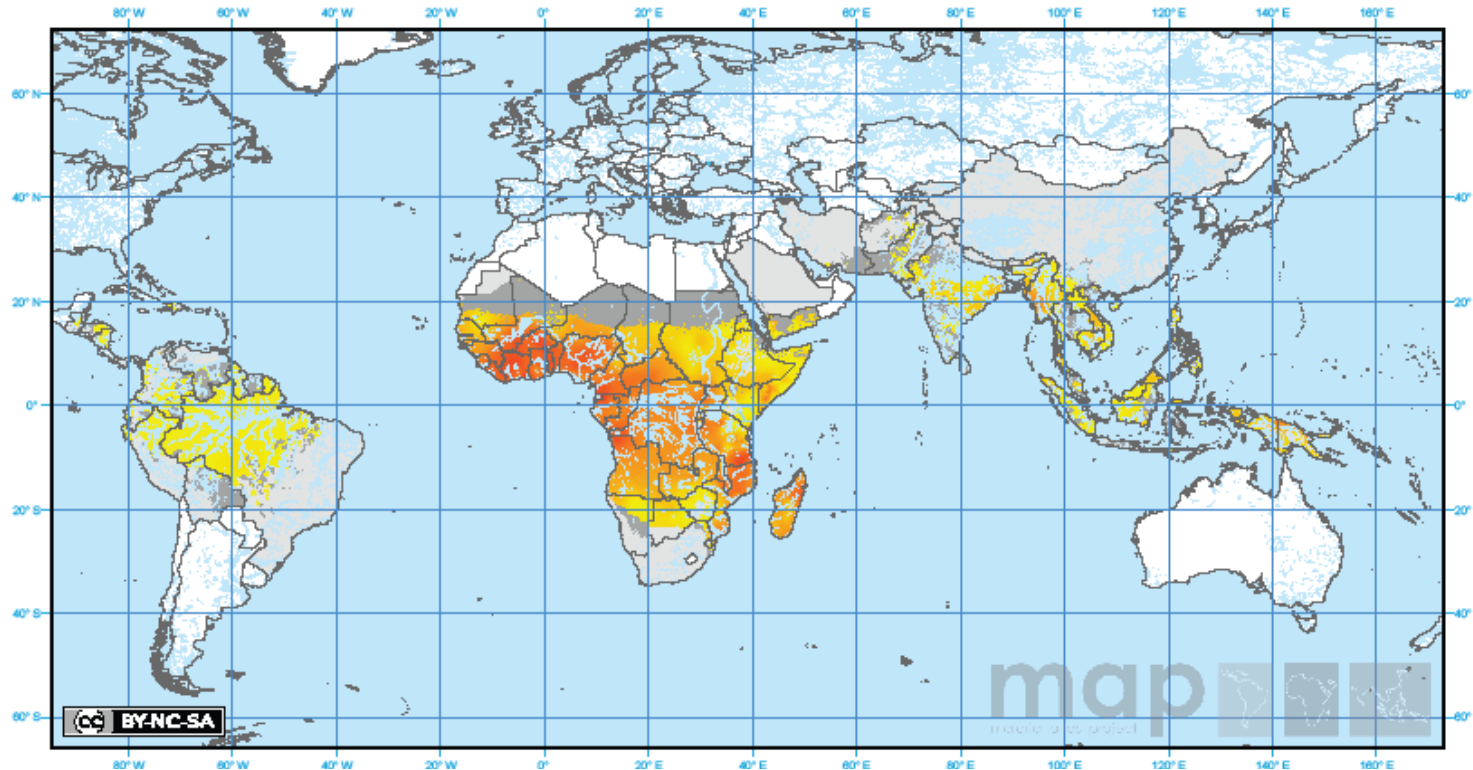
malaria programme

Novel interaction seems to be essential for invasion



- Not all interactions are created equal?
- Good candidate for drug/vaccine

What are the big problems?



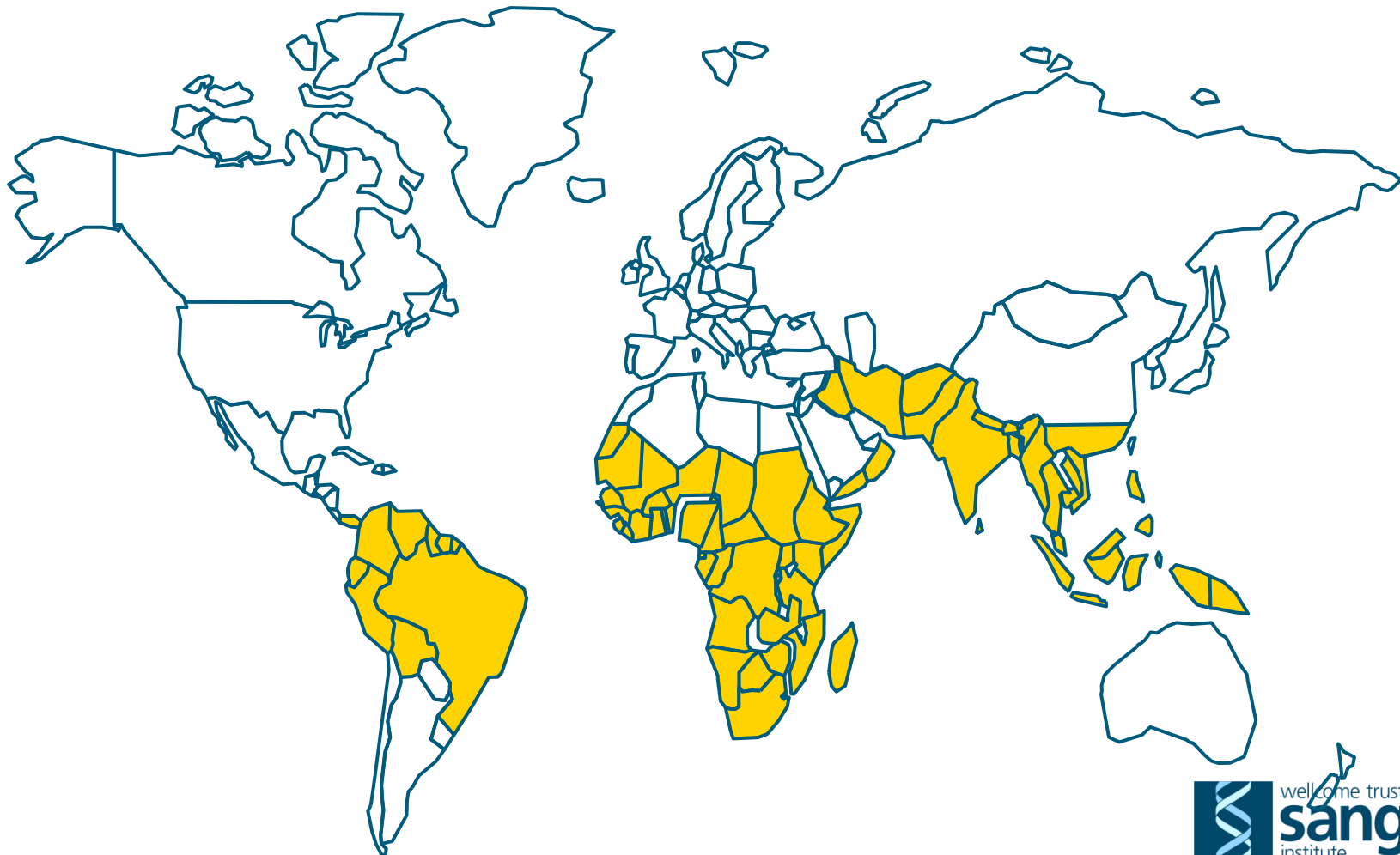
- *Plasmodium* parasites are smart, but...
- We have had good drugs for more than 60 years, useable ones for more than 300
- Why is malaria still around?

Image licensed to the Malaria Atlas Project (MAP; www.map.ox.ac.uk) by Hay, S.I. et al. (2009). A world malaria map: *Plasmodium falciparum* endemicity in 2007. *PLoS Medicine* 6(3): e1000048.

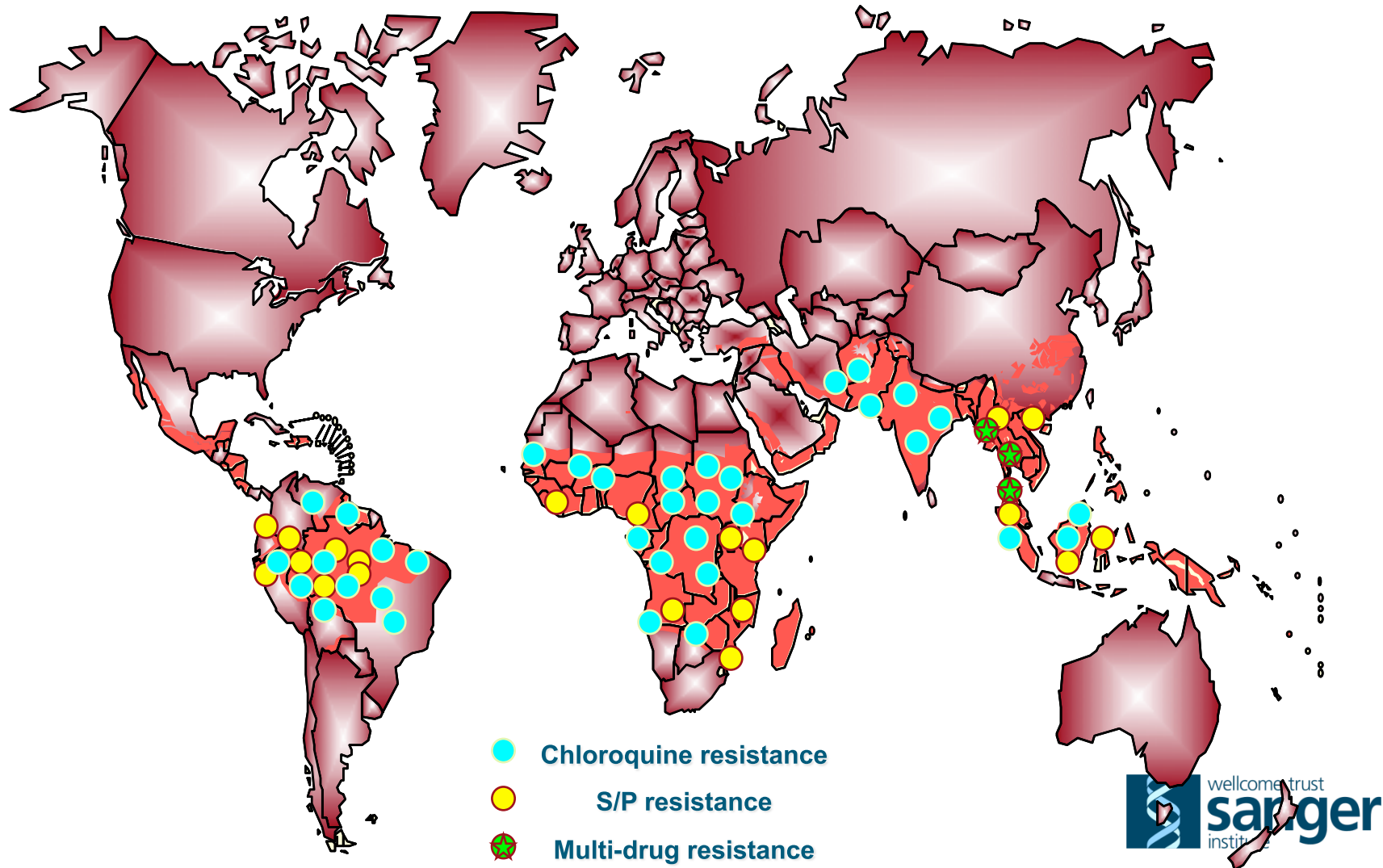
Spread of drug resistance - Chloroquine 1960



Spread of drug resistance - Chloroquine - 1999



Spread of drug resistance - State of play 1999



malaria programme

BBC NEWS

You are in: **Health**
Saturday, 17 November, 2001, 10:05 GMT

New drug hope for malaria



Resistance to anti-malarial drugs is a major concern

Experts believe a powerful Chinese herbal remedy for malaria could be combined with modern drugs to crack the disease.

Every year one million children die from the disease, and there are an estimated 300 million cases world-wide.

Resistance to anti-malarial drugs is causing a major concern especially in Africa and some of the poorer nations that are more susceptible to the disease.

“ These new treatments could save thousands of lives every day ”

Dr Shigeru Omi
WHO

See also:

- 14 Nov 01 | Health
Garlic 'fights malaria'
- 11 Oct 01 | Health
Malaria drug could 'beat resistance'
- 01 Jun 01 | Health
Herb offers malaria treatment hope
- 16 Oct 98 | Health
Can a Chinese herb win the malaria war?

Internet links:

- Public Health Laboratory Service
- World Health Organisation

The BBC is not responsible for the content of external internet sites

Top Health stories now:

- Postcode lottery in GP services
- IVF mix-up heads for court
- Transplant first for cancer patient
- Costly wait with dementia symptoms
- Chicken checked for BSE
- New hope for Aids vaccine
- Campaign to end stigma of mental illness

malaria programme

NEWS

LIVE BBC NEWS CHANNEL

Page last updated at 23:15 GMT, Thursday, 28 May 2009 00:11 UK

[E-mail this to a friend](#) [Printable version](#)

Fears for new malaria drug resistance



The drug resistance was first detected in Pailin province in western Cambodia

By Jill McGivering
BBC World Service, Cambodia

In a small community in Western Cambodia, scientists are puzzling over why malaria parasites seem to be developing a resistance to drugs - and fearing the consequences.

Ten days ago, Chhem Bunchhin, a teacher in Battambang Province, became ill with chills, fever, headache and vomiting. At a nearby health centre he was treated with drugs.

SEE ALSO

- Doctors welcome malaria microchip
24 Apr 09 | Glasgow, Lanarkshire and West
- 'Double whammy' malaria drug hope
10 Apr 09 | Health
- Malaria 'early warning' test hope
08 Dec 08 | Health
- Technology to eradicate malaria
19 Nov 08 | Health
- Human malaria jab tests nearing
04 Aug 08 | Health
- 'Breakthrough' in malaria fight
14 Jul 08 | Health

RELATED BBC LINKS

- BBC malaria

RELATED INTERNET LINKS

- Afrims
- Mahidol-Oxford Tropical Medicine Research Unit
- WHO Cambodia
- Cambodia Ministry of Health

The BBC is not responsible for the content of external internet sites

TOP ASIA-PACIFIC STORIES

News Front Page

World



- Africa
- Americas
- Asia-Pacific**
- Europe
- Middle East
- South Asia

UK

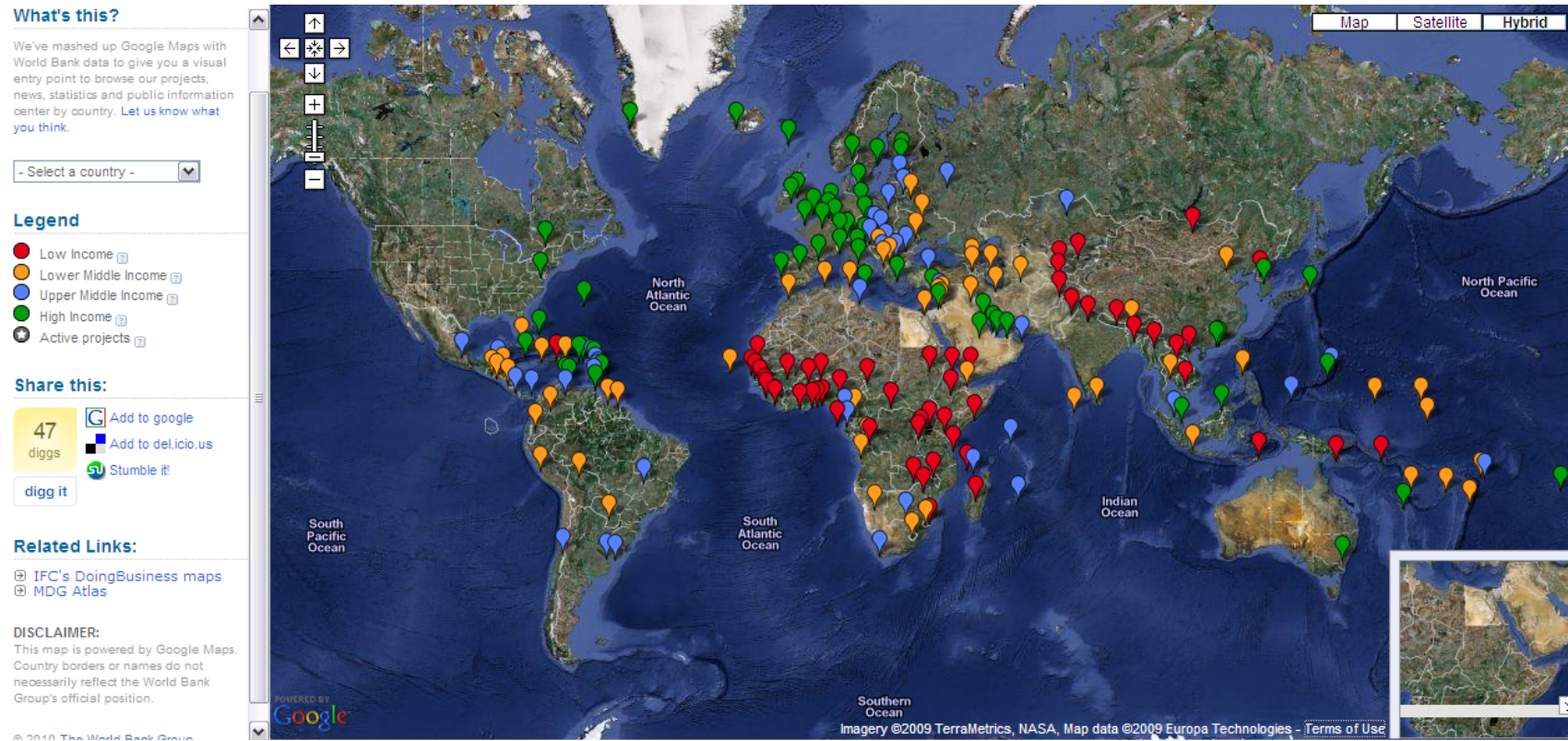
- England**
- Northern Ireland
- Scotland
- Wales
- Business
- Politics
- Health
- Education
- Science & Environment
- Technology
- Entertainment
- Also in the news

Video and Audio

- Have Your Say
- Magazine
- In Pictures
- Country Profiles
- Special Reports

Related BBC sites

Economics



Source and copyright owner of data: International Bank for Reconstruction and Development, The World Bank

Economics

Country	1997	2001	Change
Burkina Faso	7	6	-14%
Zambia	24	19	-21%
India	23	24	+4.3%
Sweden	2300	2150	-6.5%
U.S.A.	3939	4887	+24%

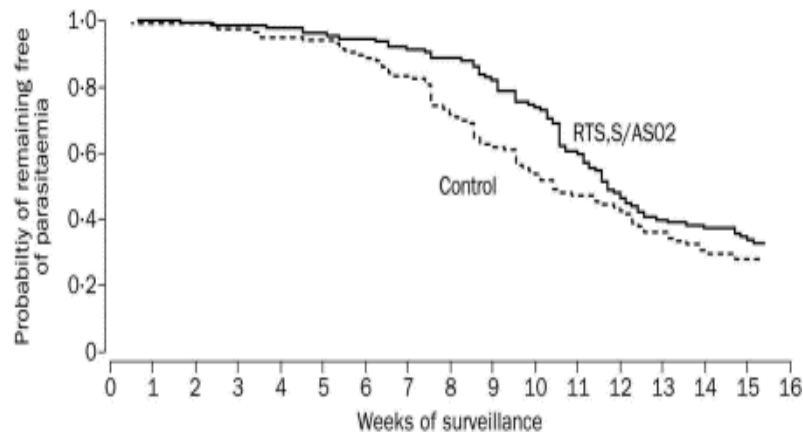
Per capita annual health expenditure (WHO 04)

malaria programme

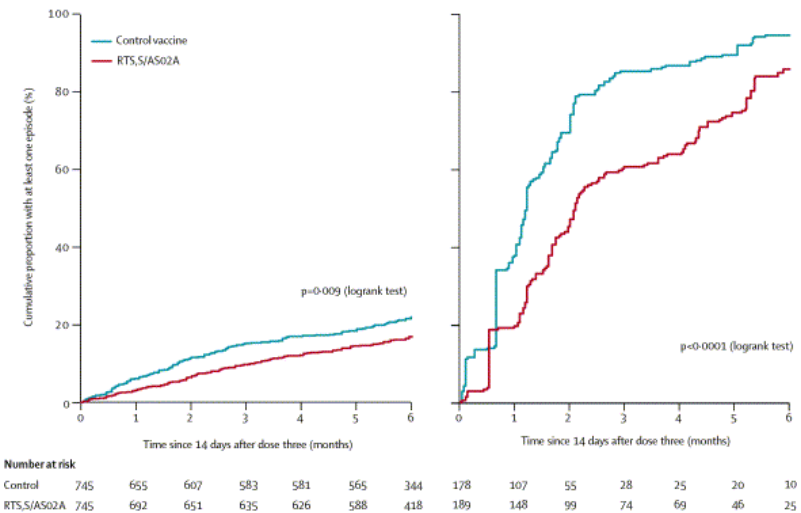
A vaccine - coming soon?

Malaria vaccines are complicated

- No comparable eukaryotic vaccine ever developed
- Multiple stages/targets and long evolutionary history
- Best vaccine (going to Phase III) is only 50% effective at best



Number at risk									
RTS,S/AS02	131	129	125	118	110	90	58	45	
Control	119	118	110	101	82	60	47	33	



Number at risk														
Control	745	655	607	583	581	565	344	178	107	55	28	25	20	10
RTS,S/AS02A	745	692	651	635	626	588	418	189	148	99	74	69	46	25

Image source: Bojang et al The Lancet 2001, Vol 358, (9297):1927-34, Fig 3;
Alonso et al The Lancet 2005, Vol 366, (9502):2012-8, Fig 2

Why are malaria parasites so successful?

Julian Rayner
Sanger Institute Malaria Programme
julian.rayner@sanger.ac.uk

